CHEMOTHERAPY OF EYELID AND PERITORBITAL TUMORS*

BY *Malcolm N. Luxenberg,* MD AND (BY INVITATION)
Troy H. Guthrie, Jr, MD

INTRODUCTION

BASAL CELL CARCINOMA (BCC) IS THE MOST COMMON MALIGNANT TUMOR OF THE eyelids and periorbital tissues with a peak incidence in the seventh and eighth decades and is 40 times more common than squamous cell carcinoma (SCC), the second most frequent malignant lesion involving these tissues. BCC occurs most often on the lower eyelids and medial canthal area with lesions in the latter location being prone to infiltrate deeply and may invade the orbit making management more difficult. There are multiple methods of treatment for these tumors including: surgical excision, chemosurgery, cryotherapy, and radiation therapy. Surgical resection is the preferred method in most cases and the cure rate with this technique is excellent. Unfortunately, some patients refuse surgery while others are not good surgical candidates due to significant medical problems or the surgery will result in extensive disfigurement with potential loss of useful ocular function. Radiation therapy can be effective for many lesions but should be used with caution since large tumors and those located in the medial canthal area may recur on the deep margin and be difficult to detect, especially in the early stages. Serious ocular side effects may result from this form of therapy and a well trained radiation therapist and appropriate equipment is needed. In addition, the usual course of radiation therapy requires 5 to 6 weeks to complete and is logistically difficult for some patients. Cryotherapy is useful for smaller lesions but is less effective for larger and deeply invasive tumors.

Because of these limitations development of other forms of treatment, such as chemotherapy, would seem to be warranted for the management of certain complicated cases, especially those with large or deeply inva-

*From the Departments of Ophthalmology and Medicine (Division of Hematology/Oncology), Medical College of Georgia, Augusta, GA.

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sive lesions. Systemic chemotherapy for these lesions may eradicate the tumor or produce a partial remission (PR) with reduction in size of the lesion so that other modes of therapy are more effective. A smaller residual tumor may permit complete removal with less extensive surgery, more effective radiation therapy with smaller fields or local treatment with iontophoretic chemotherapy.

The successful treatment of localized and metastatic BCC and SCC with chemotherapy has only recently been reported.[1-3] These preliminary studies using cisplatin-based combination chemotherapy have shown initial promising results in the management of lesions of this type. The present group of patients represents the largest known series with BCC or SCC of the periorbital tissues treated successfully with systemic chemotherapy, and to our knowledge, this is the first report of the use of iontophoresis in the management of lesions of this type.

MATERIALS AND METHODS

Between September 1980 and September 1984, 15 patients with advanced, biopsy-proven BCC or SCC were treated with systemic cisplatin-based combination chemotherapy. Of these 15 patients, 8 had primary or recurrent lesions involving the eyelids and/or periorbital tissues with six of the tumors being BCC and two of them being SCC. In addition to the systemic chemotherapy in these eight patients, five residual or recurrent tumors in three of these patients were treated with the local application of cisplatin by iontophoresis. Surgical excision was ultimately required in two patients and radiation therapy was needed in three patients for persistent disease following chemotherapy. This paper reports our experience in the treatment of these eight patients with chemotherapy.

All patients were seen at the Medical College of Georgia or associated hospitals, and were followed by a medical oncologist, and all but two of the eight patients with ocular lesions were seen by an ophthalmologist. The patients ranged in age from 62 to 85 years with an average age of 69 years. There were four women and four men.

Each patient had a complete history and general medical examination as well as an ophthalmologic evaluation, except in the two patients noted. All lesions were biopsy-proven BCC or SCC and the size was documented by measuring two or more perpendicular diameters and/or changes noted on roentgenographic studies. Response to therapy was documented by repeat measurement of the lesions, follow-up x-ray studies, serial photographs, and when possible, a repeat biopsy was obtained. Routine laboratory tests before the initial course of therapy included an automated

blood and platelet count, a screening blood chemistry (SMA-18), serum creatinine, urinalysis, chest x-ray, electrocardiogram, and in most patients, a 24-hour creatinine clearance. All of these tests except the chest x-ray and electrocardiogram were repeated before each subsequence courst of therapy. A follow-up creatinine clearance was obtained only if the serum creatinine was rising.

Seven patients received combined systemic chemotherapy administered by an oncologist, consisting of cisplatin (Platinol) 75 mg/m^2 (body surface area) and doxorubicin (Adriamycin) 50 mg/m^2 given intravenously at 3- to 4-week intervals and one patient received cisplatin alone in a dose of 80 mg/m^2. One patient received two separate courses of therapy, 1 year apart, resulting in nine courses of therapy in eight patients. All patients were admitted to the hospital for treatment and were kept carefully hydrated with mannitol and saline infusions while receiving chemotherapy to avoid cisplatin-induced nephrotoxicity. No patient has received more than four concurrent courses of systemic chemotherapy and no serious side effects from the treatment have been observed.

In three of the eight patients, 5 to 10 mg of cisplatin was delivered directly to five lesions (all BCC) using iontophoresis with the therapy usually being given on a daily basis with the interval between treatments ranging from 1 to 21 days. The maximum number of treatments given was nine. An iontophoresis system (Dentelect Electroapplicator system, Model C-2, Dentelect Corp, Augusta, GA) (Fig 1) utilizing the technique described by Gangarosa et al[4,5] was used to deliver cisplatin into the tumor(s) using direct current. The treatment (active) electrode, covered with a hollow, plastic tip filled with cotton soaked in a solution of distilled water containing 5 to 10 mg of cisplatin was placed over the lesion. A direct current of between 0.5 to 1.5 mAmps, depending on the size of the lesion, was used to deliver the drug to the lesion over a period of 20 minutes using a positive electrode (anode). The return (negative) electrode, using 1% sodium nitrate as the indifferent electrolyte, was placed on the patient's arm. This mode of therapy was easy to use and well tolerated with no apparent significant side effects noted.

Criteria for response to therapy were defined as follows: complete remission (CR), disappearance of all measurable lesions for a minimum of 1 month; PR, greater than 50% reduction in size of all lesions of at least 1 month's duration; and no response (NR), less than 50% reduction in size of measurable lesions. The duration of response was measured from initiation of chemotherapy to progression of disease or the last time of observation. An adequate trial of therapy was defined as at least one course of chemotherapy and a follow-up period of 4 weeks.

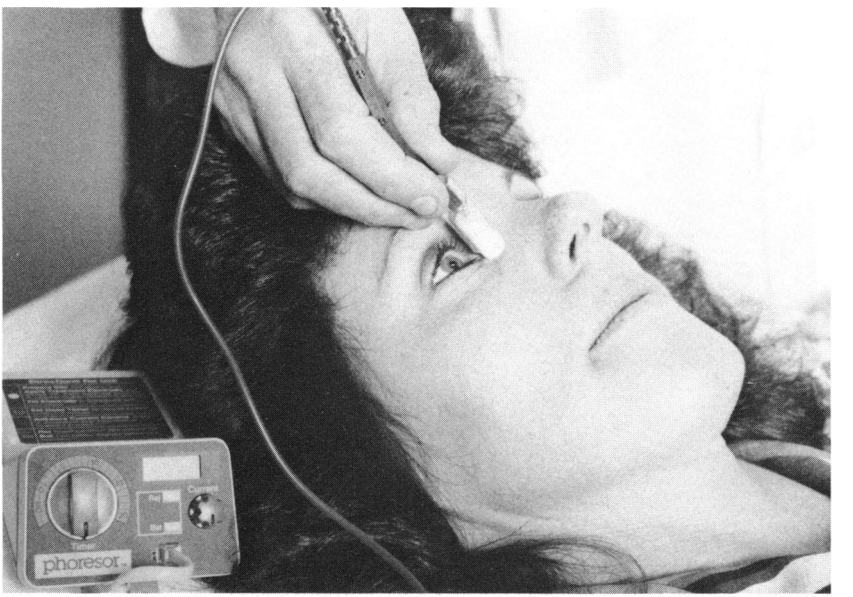

FIGURE 1
Iontophoretic therapy.

CASE REPORTS

CASE 1

CB, a 66-year-old white woman, was referred in September 1980 for treatment of a SCC of the left temporal region which had been incompletely excised in March 1980. Examination revealed an 8 × 12 cm cystic mass between the left lateral canthus and ear. The patient received two courses of cisplatin 75 mg/m^2 and doxorubicin 50 mg/m^2 in September and October 1980 with total resolution of the lesion. Subsequently, 6000 rads of prophylactic radiation therapy was given to the tumor bed in November and December 1980. The patient did well until August 1981 when a 4 × 6 cm recurrence developed. Two additional courses of chemotherapy with cisplatin 75 mg/m^2 and doxorubicin 50 mg/m^2 were given in August and September 1981 with a PR. Residual tumor was surgically excised in August 1981 and there has been no subsequent recurrence over a period of 35 months.

CASE 2

LM, a 70-year-old white man, was first seen in November 1980 with a history of recurrent BCCs involving the right medial canthus and nose. Five years earlier, he had undergone a left maxillectomy and orbital exenteration plus radiation therapy for BCC. Examination revealed an elevated, pink, firm, irregular 5 mm

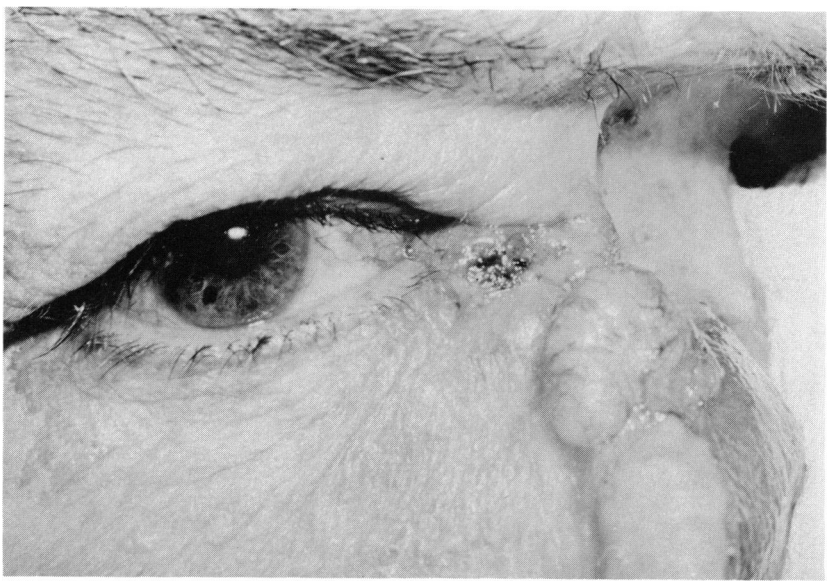

FIGURE 2
Case 2: Pretreatment appearance of lesions (SCC).

lesion in the right medial canthus and a similar 12 × 15 mm lesion on the dorsum of the nose. There was edema of the eyelids and conjunctiva and resistance to retropulsion of the globe. Computerized tomographic scans revealed a soft tissue mass in the right anterior nasal cavity with involvement of the anterior ethmoid and maxillary sinuses on the right with bone destruction (possibly related to previous surgery) in these areas. Erosion of the medical wall of the right orbit with lateral displacement of the eye was noted. Two courses of chemotherapy with cisplatin 75 mg/m^2 and doxorubicin 50 mg/m^2 were given in January and February 1981 with resolution of all visible tumor and return of normal ocular function. Two new small tumors (one on the right cheek and one on the nose) were treated by iontophoresis using cisplatin in March 1984. There was 90% resolution of the lesion on the nose and PR of the cheek lesion with residual tumor at the latter site being excised surgically. The patient was last examined in April 1985 and there was no evidence of tumor recurrence (Figs 2 and 3).

CASE 3

JB, a 71-year-old white man, was initially examined in February 1983 with a history of having had a BCC incompletely excised from the nose and right medial canthus in December 1982. Examination revealed a 2 × 3 cm ulcerated lesion of the right medial canthus and bridge of the nose and there was a cicatricial

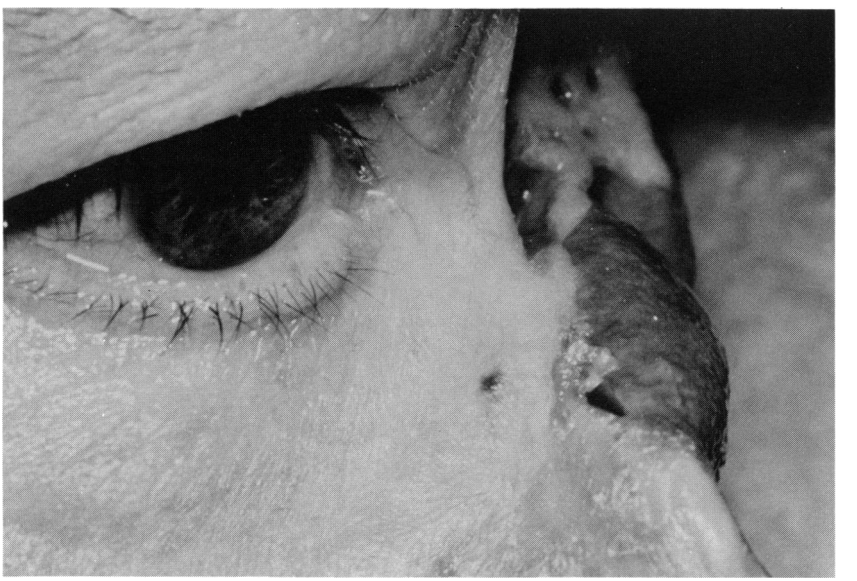

FIGURE 3
Case 2: Appearance 44 months after systemic chemotherapy.

ectropion of the medial portion of the right lower eyelid. Three courses of chemotherapy with cisplatin 75 mg/m^2 and doxorubicin 50 mg/m^2 were given in January and February 1983. All visible tumor resolved and the patient remained in remission until June 1984 when a small, suspicious lesion was seen in the right medial canthus. A biopsy of the lesion demonstrated recurrent BCC. In July 1984 the patient received a series of three iontophoretic treatments with 5 to 10 mg of cisplatin iontophoresed directly into the tumor. There was partial resolution of the lesion and a repeat biopsy in September 1984 revealed persistence of the BCC. The patient refused surgical excision of the lesion. He was treated with radiation therapy in October and November 1984 and received a total dose of 5500 rads. He was last examined in March 1985 and there was no evidence of tumor recurrence at that time. Computerized tomography scans done at that time revealed no evidence of tumor.

CASE 4

PL, an 85-year-old white woman with organic brain syndrome, was initially evaluated in February 1983. She was referred for treatment, after having previously refused surgery, of an extensive BCC involving the right eyelids and periorbital region of unknown duration. A massive lesion of the right eye involving the eyelids, medial and lateral canthi, bridge of the nose and eyebrow was noted on

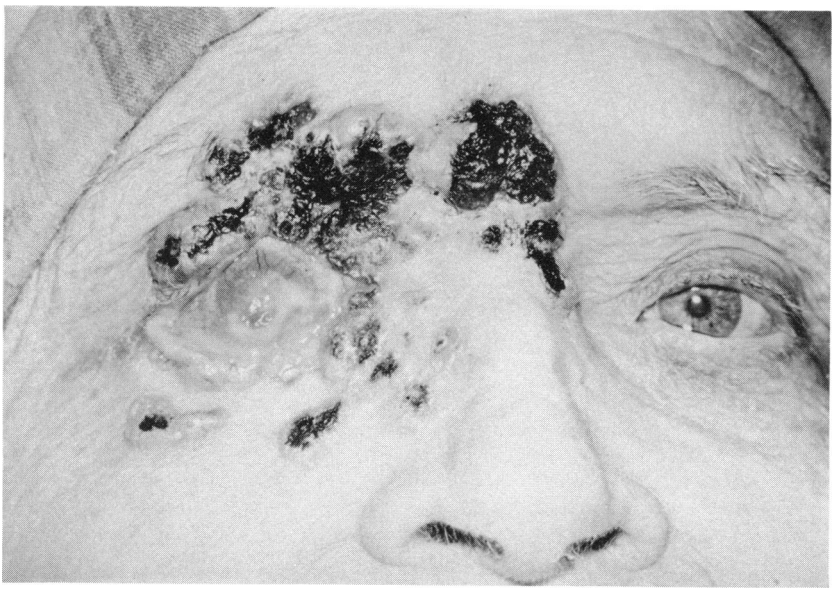

FIGURE 4
Case 4: Lesion (BCC) involving eyelids and periorbital tissues of right eye prior to treatment.

examination. There was severe cicatricial ectropion of the eyelids and lagophthalmos as well as keratinization of the conjunctiva and cornea with associated scarring and decreased vision. The patient received two courses of systemic chemotherapy with cisplatin 75 mg/m^2 and doxorubicin 50 mg/m^2 in March 1983 with a 90% reduction in size of the tumor masses. The patient then refused further therapy of any type. On examination in February 1984 two new small lesions were noted in the right medial canthus and biopsy of these revealed BCC. She was last examined in November 1984 and no further changes were noted. In spite of recurrent tumor, the patient has done quite well with no apparent further damage to the eye (Figs 4 and 5).

CASE 5

MC, a 62-year-old white woman, was first seen in August 1983 with a history of known BCC of approximately 15 years' duration for which she had refused treatment. On examination, a massive lesion of the left face, measuring approximately 7 × 10 cm with involvement of the eyebrow, upper eyelid, and lateral canthal region was noted. A 15 × 25 mm lesion was also present in the left medial canthal area. Three courses of systemic chemotherapy with cisplatin 75 mg/m^2 and doxorubicin 50 mg/m^2 were given in November and December 1983 and January 1984

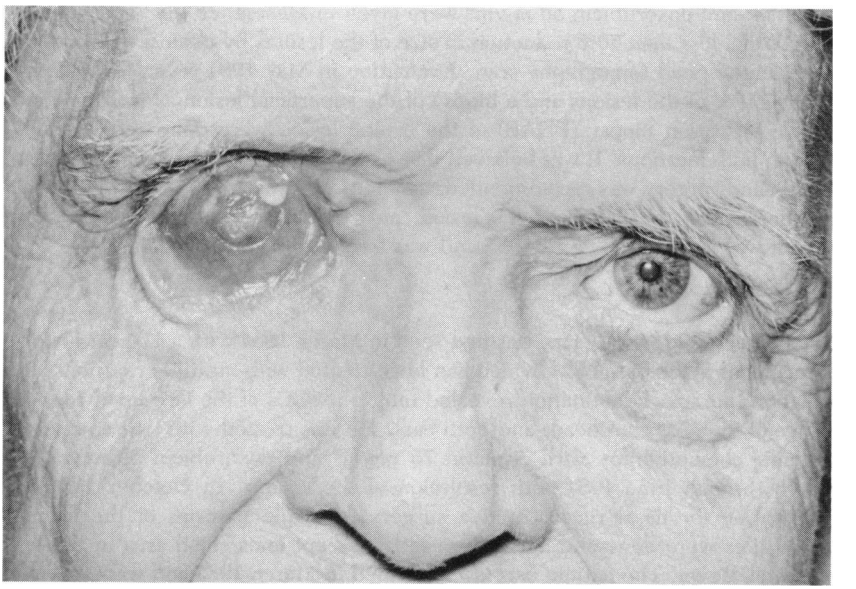

FIGURE 5
Case 4: Appearance 11 months following two courses of systemic chemotherapy.

with a 50% reduction in tumor volume. The patient refused further systemic chemotherapy because of gastrointestinal side effects related to the treatment. In February 1984, eight iontophoretic treatments with 5 to 10 mg of cisplatin were given to two residual lesions with a PR. In March 1984, 6000 rads of radiation therapy was administered for residual disease with complete clinical remission of the tumors. The patient refused to return for further follow-up and she was last examined by her radiation therapist in Macon, GA in January 1985 and he noted no recurrence of the lesions at that time.

CASE 6

OC, a 70-year-old white woman, was referred for evaluation in November 1983 with a 6-year history of BCC of the left medial canthus, left medial eyebrow, and bridge of the nose which had been resected on three previous occasions. On examination a 5 × 7 mm firm, pinkish, elevated, cystic lesion was noted in the left medial canthus and a second 5 × 8 mm firm lesion, fixed to bone, was palpated in the superior nasal orbit. A biopsy of the superficial lesion revealed BCC. Computerized tomography scans of the orbit demonstrated a moderate sized lesion in the anterior portion of the superior nasal orbit with no bony changes. The patient requested nonsurgical therapy and three courses of chemotherapy with cisplatin

75 mg/m^2 and doxorubicin 50 mg/m^2 were given in December 1983 and January 1984 with a less than 50% reduction in size of the lesions by clinical examination and computerized tomography scan. Evaluation in May 1984 revealed apparent enlargement of the lesions and a biopsy of the superficial lesion as well as a fine needle aspiration biopsy (FNAB) of the orbital lesion were done and revealed BCC in both locations. It was believed that further chemotherapy would be of no benefit and surgery was recommended. The left orbit was explored in May 1984, and because of the extent of the lesion, an exenteration was performed. The patient was last seen in April 1985 and was free of disease at that time.

CASE 7

RP, a 66-year-old white man, was first seen in March 1984 with a 17-year history of recurrent SCCs of the face which had been treated with multiple excisions and radiation therapy. Examination revealed multiple SCCs of the face involving the bridge of the nose, forehead, and both ears. He was treated with four courses of systemic chemotherapy with cisplatin 75 mg/m^2 and doxorubicin 50 mg/m^2 in March through June 1984 with resolution of the lesions. In October 1984, in preparation for nasal reconstructive surgery, multiple biopsies of the former tumor sites were done and all were negative except for a small area in the left temporal region. The patient was last examined in March 1985 and was clinically free of disease and refused further treatment.

CASE 8

HS, a 64-year-old white man, was first evaluated in June 1984 with a 3-month history of swelling, pain, and tenderness in the right medial canthal region which he thought was due to an insect bite. On examination, the skin and superficial tissues in the right medial canthal area were noted to be contracted with secondary tightening and medial displacement of the eyelids as well as ptosis of the right upper eyelid. A firm, smooth mass measuring approximately 10 × 18 mm was palpated along the inferior and medial orbital rim. No definite superficial tumor was seen. Moderate resistance to retropulsion of the globe and 3 mm of proptosis on the right were noted (Fig 6). Computerized tomography scans demonstrated a large lesion in the right medial orbit (Figs 7 and 8). A FNAB of the orbital lesion was done and revealed malignant cells consistent with BCC. The patient elected to have nonsurgical treatment and three courses of chemotherapy using only cisplatin 80 mg/m^2 were given at intervals of 3 weeks in July and August 1984. The patient noted a decrease in size of the lesion 1 week after the first course of therapy with further continued improvement over the next few weeks. He was last examined in October 1984 and the contraction of tissues in the right medial canthus, resistance to retropulsion, and exophthalmos were no longer present and the medial orbital mass could not be palpated (Fig 9). A computerized tomography scan done at that time revealed resoluton of the orbital mass lesion (Fig 10). Since the last examination, the patient has not kept scheduled follow-up appointments. A telephone conversation with him in May 1985 suggests there has been no recurrence of the tumor.

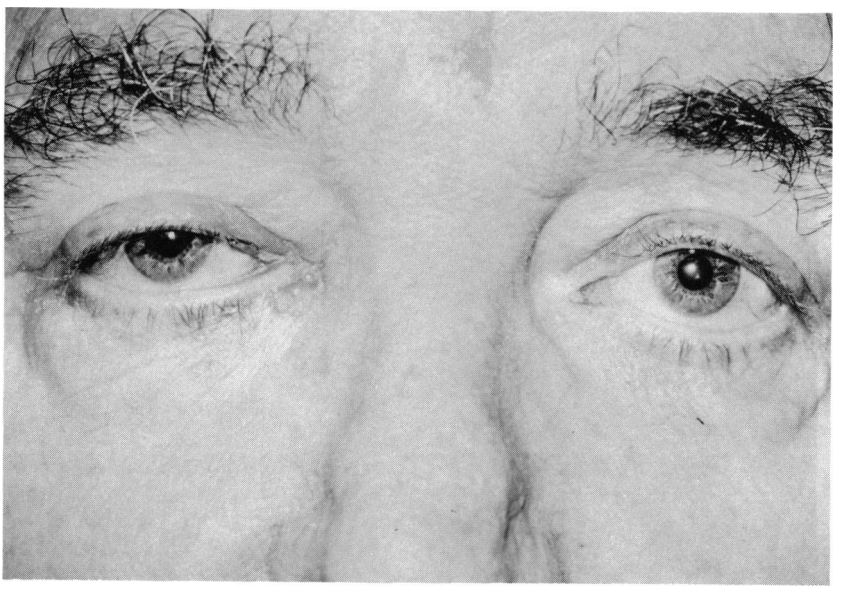

FIGURE 6
Case 8: Right medial canthal lesion (BCC) shortly after first course of treatment.

RESULTS

In this series, eight patients (nine lesions) were treated with systemic chemotherapy using either cisplatin alone or combined with doxorubicin for BCC and SCC of the eyelids and periorbital tissues. One patient with SCC was treated a second time, 1 year after the initial therapy, for a recurrent lesion. Responses of the lesions to treatment were as follows: five had a CR, three had a PR, and one had NR. Responses to chemotherapy were usually noted within 1 to 2 weeks after beginning treatment and improvement often continued for up to 6 weeks after completion of therapy. The range of follow-up is 2 to 50 months with the average being 21 months. One patient has been followed only 9 months and another only 2 months with all the rest having been followed a minimum of 12 months since completion of chemotherapy. In three of the eight patients, there was an initial response to systemic treatment with subsequent recurrence of the lesion(s). Case 4 had a dramatic improvement, and although there is some recurrent tumor, further ocular damage has been averted and her appearance is considerably improved. Three of the patients subsequently received radiation therapy for residual or recurrent

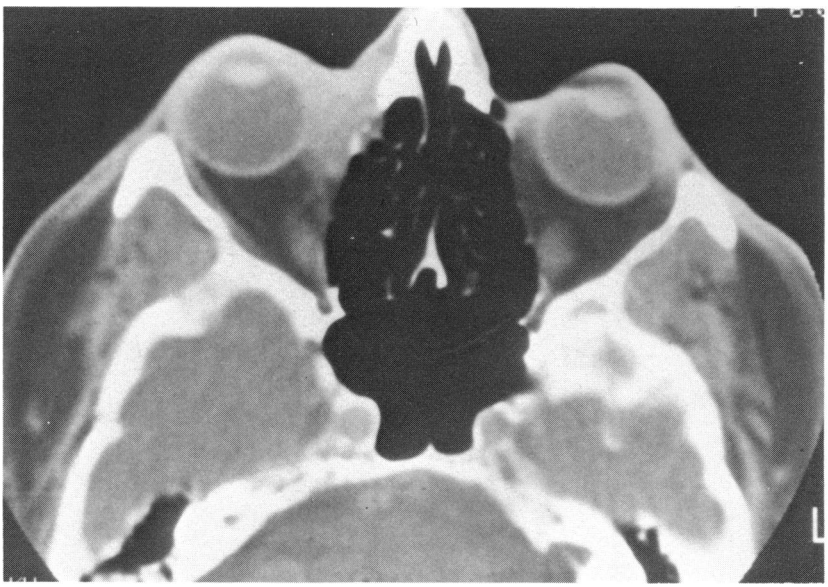

FIGURE 7
Case 8: Computerized tomography scan prior to treatment demonstrating mass lesion in right medial orbit.

lesions and two patients required surgical excision for control of residual tumor. However, as a result of reduction in size of the initial lesion(s) from chemotherapy, the amount and size of the fields of any required radiation therapy or surgery was reduced. Three of the eight patients developed five new or recurrent tumors and were treated with iontophoretic therapy using cisplatin with a PR of all five lesions.

The only adverse reactions encountered from systemic therapy were alopecia and gastrointestinal disturbances which occurred in seven patients. Both of these side effects resolved completely after cessation of therapy. There were no instances of drug-induced cardiac or renal toxicity which is noteworthy in this elderly group of patients. No adverse reactions were observed from the iontophoretic application of cisplatin. The results of radiation therapy were unaffected by prior chemotherapy.

DISCUSSION

Large and deeply invasive BCC and SCC are often difficult management problems and in some cases they may not be amenable to current stan-

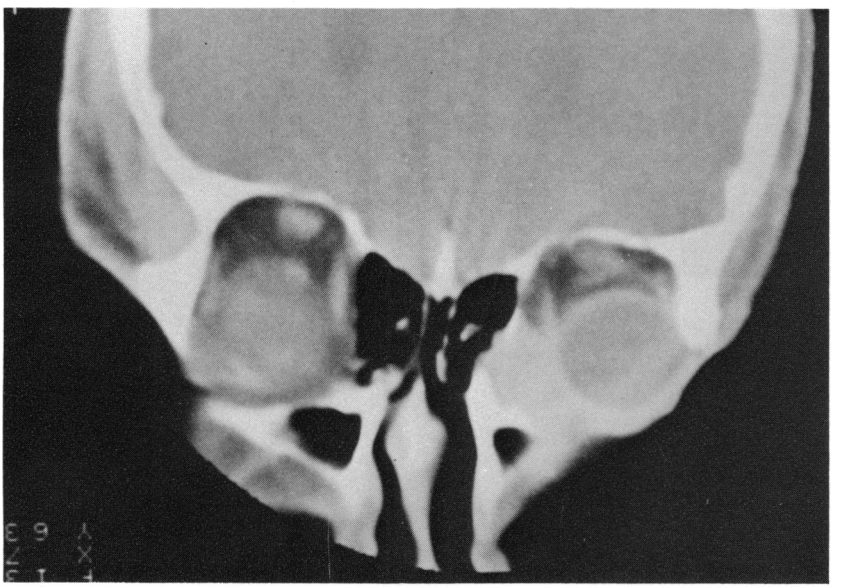

FIGURE 8
Case 8: Computerized tomography scan (coronal view) of right orbital lesion prior to treatment.

dard methods of treatment. In these situations, alternate modes of treatment, such as chemotherapy, may result in remission of the tumor or a significant decrease in size which then allows other methods of treatment to be used. Chemotherapy should be used judiciously and only in selected cases due to the potentially serious adverse reactions from these drugs and should be administered under the direction of an oncologist. Significant reactions seen with cisplatin are: nephrotoxicity, ototoxicity, myelosuppression, and gastrointestinal effects manifested as nausea and vomiting. Serious reactions that may occur with doxorubicin include: cardiotoxicity, bone marrow depression, and alopecia which is reversible. A number of lesser reactions can be seen with either of these drugs. Serious adverse reactions are uncommon when the drugs are given and the patients carefully monitored by an oncologist. This is evidenced by the lack of significant problems in the current group of patients.

Contraindications to systemic chemotherapy with these agents are: significant renal failure with a creatinine greater than 3 or a creatinine clearance less than 50 ml/minute; uncompensated heart failure or recent myocardial infarction, and neutropenia or thrombocytopenia. Ocular and

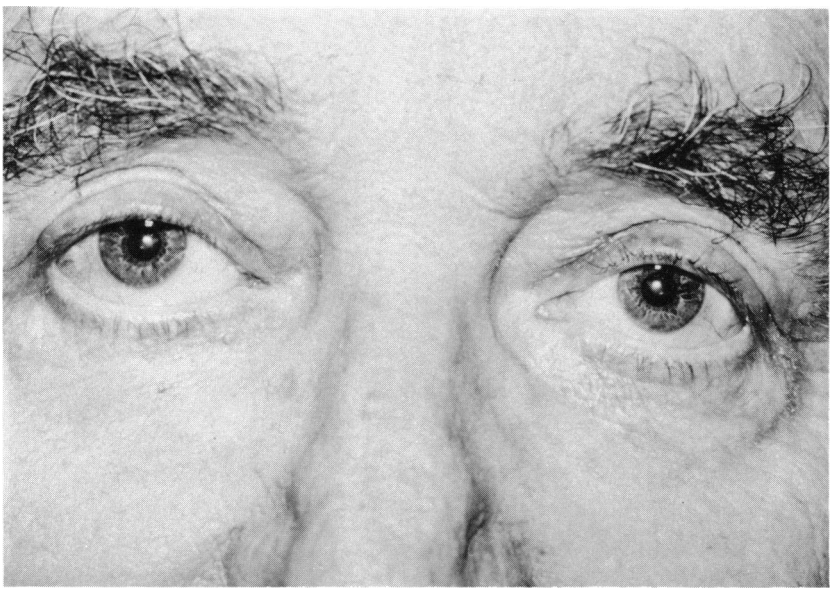

FIGURE 9
Case 8: Appearance 2 months after third course of systemic chemotherapy.

nervous system toxicity, although uncommon, has been reported in association with a variety of chemotherapeutic agents.[6,7] Those which have been observed in association with cisplatin are: peripheral neuropathy,[8] papilledema, and retrobulbar neuritis,[9,10] optic disc swelling,[11] as well as cortical blindness and visual field defects, both of which are usually transient.[12-15] A recent study of patients with brain tumors who were treated with intracarotid infusion of cisplatin revealed pigmentary changes in the retina, retinal arteriolar constriction, and optic disc pallor. In addition, electroretinographic and visual-evoked response abnormalities occurred and were noted only in the eye on the side of the carotid infusion.[16] On short-term follow-up the changes appeared to be irreversible. Although these reports suggest a relationship between the observed toxic effects and the use of cisplatin, it is possible that the adverse reactions could be related to other drugs which were sometimes used in conjunction with the cisplatin or due to the basic underlying tumor process. It may be that these toxic effects are seen only with higher doses of the drug as some of these patients received larger amounts of cisplatin as compared to our group of patients. In addition, exposure of ocular tissues to very high doses of the drug over a short period of time as with

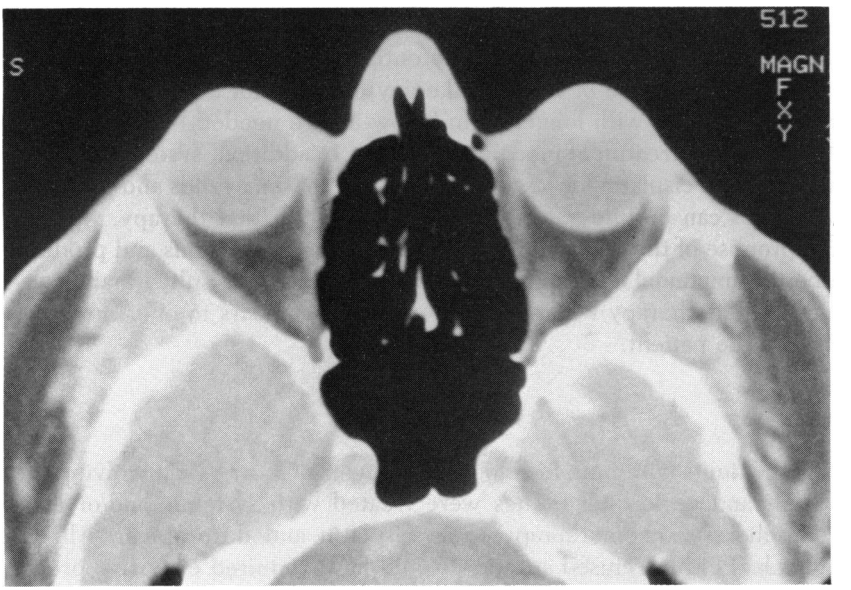

FIGURE 10
Case 8: Computerized tomography scan 2 months following third course of chemotherapy showing resolution of mass lesion in right orbit.

carotid infusion, compared to the usual intravenous administration, may be an important factor in the development of toxic side effects. Hopefully, some of these questions will be answered when larger numbers of patients have been treated with cisplatin and followed carefully for longer periods of time.

Cisplatin is now believed to be the most active component of the original two drugs used and an excellent response to this agent alone, when given systemically, was achieved in case 8. Cisplatin applied by iontophoresis has shown encouraging initial results in small lesions. However, more information needs to be obtained about the dose of drug used, frequency, duration, and timing of applications as well as number of treatment sessions. At this time, iontophoretic chemotherapy should be considered an experimental procedure and it is recommended that this not be put into widespread use until further data are available.

We conclude from this preliminary study that systemic or iontophoretic cisplatin chemotherapy for BCC and SCC, in selected patients, may induce an apparent long-term disease-free state. This may ultimately be the preferred method of treatment for patients with multiple, widespread

skin cancers, as seen with the basal cell nevus syndrome, when other forms of therapy may be difficult, potentially mutilating and noncurative. However, this mode of therapy like any other is not a panacea. Larger series of patients with longer term follow-up are needed before the true efficacy of this treatment modality is known. In addition, systemic chemotherapy with cisplatin for large BCC and SCC of the eyelids and periorbital tissues can be integrated with surgery or radiation therapy, without compromise of the second modality, to eradicate the lesions and produce a better functional and more cosmetically acceptable result. Finally, systemic chemotherapy when properly managed appears to offer no major risks to the patient.

SUMMARY

Eight patients with nine histologically proven BCC or SCC involving the eyelids and periorbital tissues were treated with systemic and/or local (iontophoresis) chemotherapy using cisplatin and doxorubicin. All patients had either refused surgery, would have required extensive procedures, or had medical problems contraindicating surgery. Systemic chemotherapy induced a CR or PR in eight of nine lesions. No patient has required maintenance chemotherapy and no significant toxic side effects were encountered. The length of follow-up ranges from 2 to 50 months. Iontophoretic therapy with cisplatin was used to treat five small foci of new, recurrent or persistent tumor(s) in three of these patients, and resulted in a partial response in all five lesions. Systemic or local chemotherapy offers an alternative to current standard forms of treatment for BCC and SCC in selected cases.

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DISCUSSION

Dr Frederick T. Fraunfelder. I would like to thank Doctor Luxenberg for allowing me to discuss this paper, and for being kind enough to allow me to review it prior to attending the meeting. Over 15 years ago, I started to work with cryotherapy in Hereford cattle for SCC of the eyelids. Within 4 years, I had done a fairly large series of humans, and came to the conclusion that cryotherapy was the treatment of choice for almost all periocular cancers. Since that time, I have realized that almost all methods have a place in the treatment of basal cells and squamous cells. This is a disease entity which requires multiple methods of treatment, from simple surgical excision to the most complicated methods, Moh's chemotherapy. Based on Doctors Luxenberg and Guthrie's work, it is now appar-

ent that we have an additional modality to use for a selected group of patients, oral chemotherapy.

In this preliminary work, the authors have shown some remarkable results in cases in which other methods of treatment might have been extremely disfiguring, or in patients who refused other forms of treatment. Whilie the authors correctly point out that this method is limited to a select group of patients, with diseases such as these, which can be mutilating, destructive to vision, and/or life-threatening, this added modality has the potential for major medical significance.

I can only encourage Doctors Luxenberg and Guthrie to continue their excellent work. I am sure they will report in the future about longer follow-up times, defining what type of cancer and conditions show the best results in order to help the patient and clinician interested in this difficult disease.

DR ROBERT E. KENNEDY. My question to Doctor Luxenberg is whether this type of chemotherapy could be handled as an out patient.

These are slides of patients who have refused treatment with these grotesque results. The lesions which are initially insignificant and painless to the patients have progressed with these "do it yourself" type of exenteration with lids, globe, orbital tissue, and marked bone erosion with these bone spicules resulting. It warrants our taking pictures initially, and then attempt to pursuade the patient to have a biopsy at least. Since some reject surgery, hospitalization, radiation, and may disappear from supervision, they may not be seen until they are in such an advanced stage that nothing is going to help.

Thinking that this type of chemotherapy might be accepted as less aggressive by the patient who has rejected surgery or hospitalization, if given on an ambulatory basis, would this be feasible? It might only be palliative in these advanced cases.

DR LEONARD APT. It may be of interest to mention some of the ocular side effects of the systemic use of cisplatin and doxorubicin. I would like to hear Doctor Luxenberg's experience in this regard.

Cisplatin (cisdiamminedichloroplatinum II, cis-Platinum II, Platinol) may cause serious undesirable effects, namely optic neuritis (usually retrobulbar), papilledema, pseudotumor cerebri, and cortical blindness. Improvement or total recovery can be brought about by discontinuing the drug or by reducing the dosage. Kaplan and Wiernik (*Semin Oncol* 1981; 9:103-130) suggested that cisplatin (a platinum-containing drug) may accumulate in the central nervous system and lead to reversible segmental nerve demyelination as seen in various forms of heavy metal poisoning. Another possible mechanism of cellular damage is the replacement of intracellular potassium ions, as shown by thallium, a heavy metal in the same seris as platinum in the periodic table.

Most recently, Miller and co-workers reported the occurrence of pigmentary retinopathy associated with cisplatin therapy (*Ophthalmology* 1985; 92:402-406). These authors pointed out that other metals such as copper, iron, mercury, and cobalt have been reported to cause pigmentary retinopathy in humans and ani-

mals (Grant WM: *Toxicology of the Eye*, 2nd ed. Springfield, Charles C Thomas, 1974, pp 39-41).

With regard to doxorubicin (Adriamycin) I know of no serious ocular toxicity. Some patients lacrimate and develop some hyperemia of the conjunctiva shortly after receiving their dose of drug. However, more serious side effects such as papilledema, pseudotumor cerebri, and cortical blindness do not occur, possibly because doxorubicin does not cross the blood-brain barrier.

I do have a specific question for Doctor Luxenberg concerning doxorubicin. Doxorubicin is commercially available as the hydrochloride salt which occurs as an orange-red crystalline powder. When given intravenously after reconstitution the drug is rapidly and widely distributed in the plasma and in tissues. The red color of the active drug persists within the body and is due to a coupling of the ribose sugar with the parent drug and its metalolites. A patient's urine has a reddish color for 1 to 2 days after doxorubicin therapy and may be mistaken for hematuria by the patient unless he is forewarned. Along this line my question to Doctor Luxenberg is: since the injected doxorubicin solution is so widely distributed throughout the body, have you observed or looked for pink or reddish tears in your patients, or have you gotten this complaint from patients or their physicians?

DR MALCOLM LUXENBERG. I want to thank Doctor Fraunfelder and the other discussants for their helpful comments. Let me respond to their questions. First, we have not noticed any contracture of tissue or other significant changes in association with the use of iontophoresis. However, it should be emphasized that this mode of therapy is still in the early stages of development and changes may be noted as our experience increases. There have been no apparent deleterious effects when both chemotherapy and radiation therapy were used and the response to treatment appeared to be the same irrespective of the sequence in which they were given. Doctor Fraunfelder raised the question of the possibility of a decreasing response to chemotherapy with subsequent courses of treatment. Thus far, this has not been noted.

Doctor Kennedy asked about outpatient treatment with chemotherapy. We would not recommend outpatient treatment as these drugs have the potential to produce serious side effects, especially nephrotoxicity with cisplatin, and these can be reduced significantly with proper selection of drug dosage and satisfactory hydration with intravenous fluids which must be given over an extended period of time. In addition, many patients develop nausea and vomiting which usually requires intramuscular or intravenous medications. We believe that the absence of any serious adverse side effects in this group of patients is, to a large extent, related to careful monitoring of the patients as outlined.

In response to Doctor Apt's questions, we are aware of the serious side effects such as optic neuritis, disc edema, cortical blindness, and visual field defects, etc, that have been reported with the use of cisplatin. The patients reported in the literature often received considerably larger doses of the drugs than received by our patients, and in some cases they were given the medication by direct intracar-

otid injections, which would potentially expose the eye to much higher doses of the drugs as compared to the usual intravenous route as used in our series. We feel that the drug dosage and route of administration used in our patients as well as careful observation and control of hydration, etc, is probably the major reason our patients have thus far not developed these complications. Lastly, we have not observed any pink or red tears in our patients. Once again, I want to thank the discussants for their comments.